PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Accompanying Divisional Application:

Applicants: David B. Anderson
Klaus K. Schmiegel
Edward L. Veehuizen

For : GROWTH PROMOTION

Docket No.: X-5683B

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents and Trademarks

Washington, D. C. 20231

Sir:

Attached is a copy of the 1449 form and Art Statement that was submitted in the parent, Serial No. 628,002. The documents describe several references relevant to the now-claimed invention. The Examiner is requested to review the list of references and to consider each listed reference during examination of the accompanying divisional application. Applicants will discuss below six references (copies supplied) which are believed most relevant. Copies of any additional references can be supplied upon request.

Applicants believe the references most closely related to the now-claimed invention are:

Van Dijk et al., Recueil, 92, 1281-1297 (1973)

Mills et al., U.S. Patent No. 4,391,826

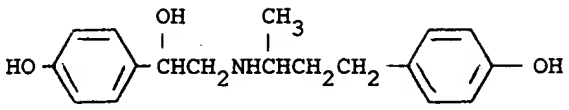
Kiernam et al., EPO 0,026,296

Kiernam et al., EPO 0,049,728

Bayer, Australian Application No. 19241/83

Mills et al., EPO 0,007,205

The parent application, Serial No. 628,002, and certain of the present claims, are limited to the use of a single compound of the formula



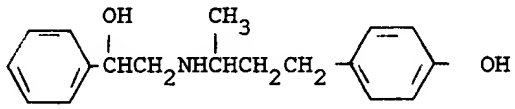
and its salts. The claims of the parent are limited to use in swine; the present claims include use in ruminants.

Van Dijk et al. discloses the compound having the foregoing structure, see Compound A5, page 1290. The compound is said to have uterospasmolytic activity.

Mills et al. in EPO 0,007,205 disclose one optical isomer of the subject compound is useful as a cardiotonic agent.

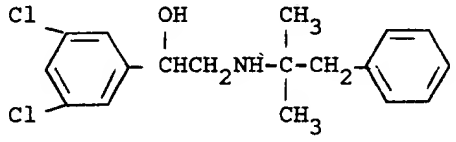
Applicants' invention includes the use of the foregoing compound to promote growth in ruminants and to improve feed efficiency in ruminants. The prior art does not disclose the claimed uses for the subject compound.

Mills et al. in U.S. Patent No. 4,391,826 describe a series of phenethanolamines said to be useful in promoting weight reduction and improving meat leanness in domesticated animals such as swine and ruminants. Mills et al. does not disclose the foregoing compound, but does describe a related compound of the formula

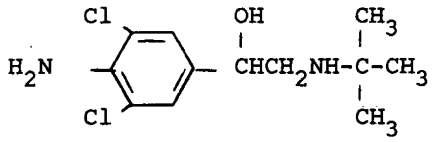


This Mills et al. compound differs in structure from the compound required by the claimed invention in the absence of a hydroxy group in the phenethanol phenyl ring. The Mills et al. teaching that such compounds effect weight loss in animals is believed directly opposite the now-claimed method of promoting growth. Applicants therefore submit Mills et al. should not preclude patenting the present invention.

Kiernam et al., EPO 26,296 and EPO 49,728 describe a series of β-phenethanolamines which are said to promote growth and improve feed efficiency in domestic animals such as swine, poultry and cattle. The references include compounds of the formulas

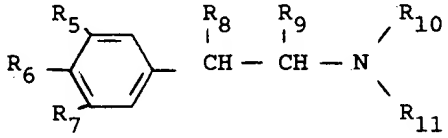


and



Applicants' invention will not permit the use of phenethanolamines having halo substitution in the phenethanol phenyl ring, or unsubstituted alkyl on the phenethanolamine nitrogen atom.

Bayer's Australian Application 19241/83 includes an extremely broad disclosure of β-phenethanolamines and their use as growth promoters for animals. The disclosure generically includes Applicants' method. See for example Claim 12 which describes use of compounds of the formula



where R_5, R_6, and R_7 can be identical or different and include hydrogen and hydroxyl; R_8 can be hydroxyl, R_9 can be hydrogen, R_{10} and R_{11} can be different and can include hydrogen and

hydroxyphenylalkyl. While the reference appears to generically include Applicants' invention, the reference fails to preclude a patent to Applicants for two reasons. First, the reference is only effective as of September, 1983. Applicants filed originally on January 31, 1983. Secondly, the Bayer disclosure is so broad and unexemplified that it really fails to disclose very much at all by way of specific teaching. There may, however, be a counterpart application pending in the U.S. Patent Office, and the Examiner is therefore alerted to consider possible interfering subject matter.

Consideration of the foregoing references and those additional references cited in the parent application is requested. Prompt and favorable action on the claims now present is solicited.

Respectfully submitted,

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December 17, 1985

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	David B. Anderson et al.	
Serial No.:	628,002	Group Art Unit: 125
Filed :	July 5, 1984	
For :	GROWTH PROMOTION	
Docket No.:	X-5683A	

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. 1.97

Commissioner of Patents and Trademarks

Washington, D. C. 20231

Sir:

As a means of complying with the duty of disclosure, Applicants submit a "List of References Cited by Applicant" on a modified PTO 1449 form and provide a copy of each of the listed references for consideration by the Examiner. The relevance of each listed reference is discussed in the following paragraphs.

Applicants submit herewith copies of several of the references that were originally cited in the parent application and upon which the Examiner based rejections under 35 U.S.C. 103. References cited in the parent application that did not form the basis of a rejection are not included in this citation. However, copies of the Information Disclosure Statements and the accompanying 1449 forms that were presented in the parent application are included herewith for the Examiner's reference. Notation that all listed references have been considered is requested.

Applicants believe the references supplied with this paper are those which are most pertinent to the examination of the invention now claimed and are most deserving of the Examiner's attention. The references supplied herewith are as follows.

EPO Application 26,298

EPO Application 49,728

South African Patent No. 3296

U.S. Patent No. 4,391,826

Van Dyke et al., Recueil, Vol. 92, page 1281-1297 (1973) and

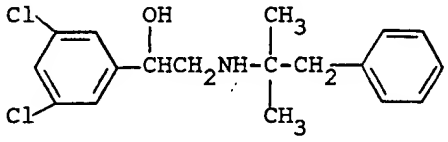
Australian Application 19241/83.

EPO Applications 26,298 and 49,728 are very similar to one another in their teaching of the use of certain β-phenethanolamines for promoting growth in domesticated animals and improving the utilization of feed. Both references also describe the alleged improvement in leanness that is realized with the use of the disclosed β-phenethanolamines. It should be noted that the 49,728 reference was published April 21, 1982. Applicants parent application was filed January 31, 1983, and the 49,728 reference was removed as a valid reference against Applicants' invention as now claimed by the filing of a declaration under 37 C.F.R. 1.131. The Examiner pointed out in the parent case that Applicants' declaration established reduction to practice only with respect to one compound, namely, the compound identified as 31537. New Claims 35 and 36 that have been presented in the above-captioned application are restricted to 31537, and accordingly it is submitted that EPO application 49,728 is effectively removed as to that subject matter.

EPO 26,298 discloses the use of a group of β-phenethanolamines for promoting growth and improving feed efficiency in animals such as swine. The reference will permit an α,α-dimethylphenethyl or benzyl grouping attached to the phenethanolamine nitrogen atom. Neither of these substituent groups are permitted according to Applicants' invention. Indeed, Applicants preferred compound 31537 requires a 1-methyl-3-(4-hydroxyphenyl)-

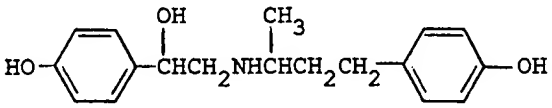
propyl substituent on the phenethanolamine nitrogen atom. EPO 26,298 does not teach or suggest any arylalkyl substituents wherein the aryl group bears a substituent, nor does the reference teach or suggest any 3-phenylpropyl substituents. Moreover, the EPO reference is directed primarily to dihalo substitution in phenethanol phenyl ring, whereas Applicants' preferred embodiment embraces only a hydroxy in that phenethanol phenyl ring.

It is believed the compound disclosed in EPO 26,298 that is most closely related in structure to Applicants' invention compounds is the compound identified as number 22 on page 38 of the reference. That compound requires a 3,5-dichloro substitution in the phenethanol phenyl ring, and requires an α,α-dimethylphenethyl substituent on the phenethanolamine nitrogen atom. The compound has the structure



EPO No. 22

Applicants' 31537 (as embraced by new Claims 35 and 36) will not permit chloro in the head ring, requires a hydroxyl group in <u>both</u> phenyl rings, and requires a 1-methylpropyl alkylene chain rather than the 1,1-dimethylethyl group of the reference. Applicants' 31537 has the structure



31537

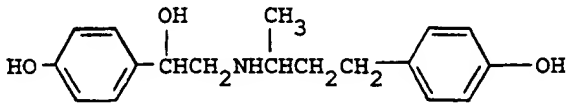
The declaration submitted under 37 C.F.R. 1.132 in the parent application, (which has been made of record in the present case) reports the results of a direct comparison of the reference compound with Applicants' preferred 31537. The declaration evidence estabishes the reference compound has only marginal

activity as a growth promoter, and has essentially no activity as an improver of feed efficiency. In contrast, Applicants' 31537 has a substantial effect both on feed efficiency and growth promotion. It is therefore submitted that Applicants' claimed invention embraced by Claims 35 and 36 is patentable over EPO 26,298.

South African Patent No. 3,296 is equivalent to U.S. Patent No. 4,391,826 issued to Mills et al. The reference teaches a group of β-phenethanolamines as antiobesity agents and also as having utility in the improvement of leanness in domesticated animals, especially swine. The Examiner suggested in the parent application that the South African reference actually disclosed 31537. The reference does not disclose 31537 for two reasons. The reference compounds are not permitted to have a hydroxyl substituent in the phenethanol or head phenyl ring. Applicants' 31537, of course, has a hydroxyl substituent in both rings. Secondly, the reference compounds which have two asymmetric carbon atoms are required to be of only one steriochemical configuration, namely, the R configuration at the carbon atom designated with the single asterisk and the S absolute steriochemical configuration at the carbon atom designated by the two asterisks. Applicants' 31537, while having the same two asymmetric centers, is not one pure isomer, but rather is a mixture of all four possible isomers.

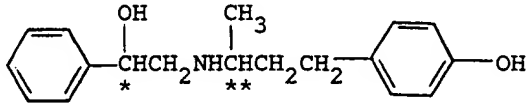
The main difference, however, between the compounds of Mills and 31537 is that 31537 is substantially more active in the promotion of growth in swine than is the Mills compound that is most closely related in chemical structure. This is amply demonstrated in the side-by-side comparative studies that are reported in the 132 declaration that was submitted in the parent

application and that is now submitted and made of record in the above-captioned application. As already pointed above, the structure of Applicants' 31537 is as follows:



31537

In contrast, the compound disclosed in the Mills reference that is most closely related in chemical structure to 31537 has the following structure:



While Applicants concede the chemical structures of these two compounds are very similar, the data presented in Table I of the 132 declaration is believed conclusive evidence that when considered as a whole, the present claims embracing 31537 are not rendered obvious by the teaching of the Mills compound. Moreover, it is not really surprising that the Mills compound is not effective as a growth promoter because the teaching in the Mills reference is that such compounds have utility as anti-obesity agents. The Mills reference presents specific data establishing that the described compounds, indeed, the very compound evaluated in Applicants' 132 declaration, caused a significant weight reduction in obese animals such as rats and dogs. It is therefore not at all surprising that the compound is ineffective in causing a weight increase when administered to animals such as swine. Applicants therefore believe that it should be clear that the use of 31537 as a growth promoter is patentable over the disclosure of Mills et al.

The Dijk et al. reference does specifically disclose 31537. Table III on page 1290 of the reference lists 31537 as

compound No. 95. The reference has little bearing upon the patentability of the invention now claimed, however, since the reference teaches nothing more than that the disclosed compounds have uterospasmolitic activity. It is believed clear that a teaching of uterospasmolitic activity bears no relationship whatsoever to the use of such compounds as growth promoters in swine.

Australian Application No. 19241/83 is cited merely to alert the Examiner to the possibility of a pending U.S. application embracing subject matter that may be overlapping with that now claimed by Applicants. See for example Claim 12 of the reference where R_{10} can be "hydroxyphenyl". The Australian application teaches the use of certain β-phenethanolamines as growth promoters and improvers of feed utilization. The reference includes a very broad generic teaching that may include some of the subject matter now claimed. The reference is not per se effective against Applicants' invention since Applicants filed well before the earliest publication date of the reference (i.e., March 28, 1984, Applicants' parent was filed January 31, 1983).

Prompt and favorable consideration of the above-captioned application in light of the references cited herein is courteously requested.

Respectfully submitted,

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January 23, 1985

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: The accompanying original application

Applicants: David B. Anderson
Klaus K. Schmiegel
Edward L. Veenhuizen

For : GROWTH PROMOTION

Docket No.: X-5683

CITATION OF REFERENCES

Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

The accompanying original application is directed to a new use for old compounds. The claimed invention includes a method for promoting growth in domesticated animals such as swine.

One of the preferred β-phenethanolamines to be employed in the claimed method is 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol. This compound, and others to be employed in the method, are described in reference AR, Van Dijk et al., Recueil, 92, 1281 (1973) (see especially compound no. 5 on page 1290). The compounds are disclosed in AR as having utero-relaxing activity. Such utility in no way suggests growth promotion as now claimed.

Reference AL[1] discloses compounds similar to those of Van Dijk et al. The AL[1] compounds are, however, specific optical isomers, and are taught as having cardiac activity and useful in physical conditioning.

Reference AA, Cox et al., U.S. Patent No. 4,086,272, generically discloses compounds such as those employed in the

present invention. The reference teaches such compounds to be heart stimulants. No mention is made of the growth promotion method now claimed.

Reference AO teaches optically active phenethanolamines (none of which are employed in the now claimed method) that are said to be useful in causing weight reduction, the exact opposite of the use now claimed. AO also teaches the disclosed compounds as improving leanness (see page 2, line 8, and page 33, line 27). The reference also discloses an animal feedstuff (see Claims 12 and 17).

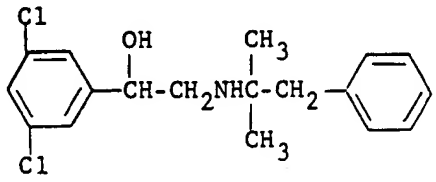
Reference AB is Ainsworth et al., U.S. Patent No. 4,338,333. The reference discloses a group of phenethanolamines that are said to be useful as "anti-obesity and/or anti-hyperglycaemic" agents. It is submitted that the very teaching of anti-obesity (i.e. weight reduction) activity for a phenethanolamine structurally similar to the compounds employed in the present method leads away from the growth promotion method now claimed.

References AC and AD describe a group of phenethanolamines that are said to inhibit lipogenesis in mammals. It is believed that the references do not affect the patentability of the claimed method for two reasons. First, the reference compounds are phenethanolamines that bear a benzoylethyl group on the nitrogen atom. Such group is not permitted according to the claimed invention. Secondly, it is not seen that inhibition of lipogenesis is suggestive of growth promotion, but rather is believed suggestive of weight loss as described in reference AB.

Reference AL, EPO 6735, discloses a generic group of phenethanolamines that include certain compounds to be employed in applicants' now claimed method. The reference describes such

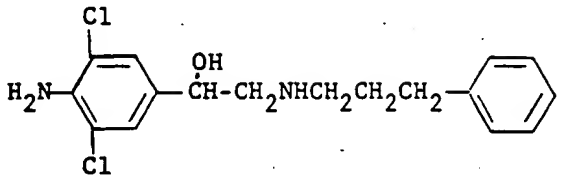
compounds as having antiobesity activity, and thus are said to be effective in causing a weight reduction. The method now claimed involves weight gain, and clearly cannot be suggested by weight reduction.

References AM and AP are perhaps the disclosures most closely related to the now claimed invention. Both references disclose certain phenethanolamines that are said to promote growth and improve leanness in animals. The reference compounds differ from those required for the present method. For example, the preferred reference compounds are 4-amino β-phenethanolamines that bear an alkyl group (e.g. tert.-butyl) on the ethanolamine nitrogen atom. Applicants' method will not permit the use of any phenethanolamine that bears an aromatic amino group or an aliphatic alkyl group on the ethanolamine nitrogen atom. While the references include a generic teaching of phenethanolamines bearing a benzyl or α,α-dimethylphenethyl group on the ethanolamine nitrogen atom (reference AP also includes phenylpropyl), there is no disclosure or suggestion of the 3-phenylpropyl-type substitution required by the now claimed invention. The only specific reference compound even remotely similar in structure to those now required is compound 22 shown on page 38 of AM, having the formula



Such compound differs structurally from those required by the present invention in that the phenethanol phenyl ring bears a 3,5-dichloro substitution, and the ethanolamine nitrogen is substituted with α,α-dimethylphenethyl. The present invention will permit neither of these substitution patterns.

Similarly, Reference AP discloses, on page 6 at lines 16-17, the compound



While the now claimed invention embraces the use of phenethanolamines bearing a 3-phenylpropyl substituent on the nitrogen atom, the invention will not permit the type of phenethanol phenyl ring substitution required by reference AP. It is therefore believed clear that nothing in either of reference AM or AP has an adverse bearing on the claims now presented.

References AN and AO are South African patents describing earlier work of one of the present co-inventors (K. K. Schmiegel) and are based upon, respectively, pending U.S. applications Serial No. 424,786 filed September 27, 1982 and Serial No. 96,361 filed November 21, 1979. The compounds disclosed in these references are similar in structure (but not identical) to those to be employed in the present method. The compounds in Reference AN are said to be useful as potentiators of known oncolytic agents. No mention or suggestion is made of the effect of such compounds on animal weight or meat quality. Reference AO describes a group of phenethanolamines that are said to be active in causing weight reduction. As mentioned above with respect to reference AL, a prior art teaching of weight reduction cannot suggest growth promotion, which is the subject of the now claimed method. In the pending U.S. application Serial No. 96,361, there is also a disclosure of a

method for improving meat leanness employing the phenethanolamines disclosed there. While the accompanying application includes leanness, the now claimed method does not employ the compounds that are the subject of Serial No. 96,361.

Copies of all of the art cited herein are enclosed for the Examiner's convenience. Consideration of all such art during examination of the accompanying application is requested. Acknowledgment of such consideration on form 1449 is requested. Prompt and favorable action on the claims as presented is solicited.

Respectfully submitted,

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January 28, 1983